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Association between Fish Consumption and Risk of Dementia: A New Study from China and A Systematic Literature Review and A Meta-Analysis

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Abstract

Objective: To assess the association of fish consumption with the risk of dementia and its dose-response relationship, and investigate variations in the association among low, middle and high income countries.

Design: A systematic literature review and a new population based study

Settings: Urban and rural communities in China; Population-based studies systematically searched from worldwide literature.

Participants: 6981 Chinese aged ≥ 60 years in six provinces took part in a house-hold health survey of dementia in China. In addition, we searched for topic-related articles through five databases, identifying 11 eligible studies for review, including 33964 participants.

Results: In the new study of China, 326 participants were diagnosed as having dementia (4.7%); those that consumed any level of fish in the past 2 years verse not eating fish had reduced risk of dementia (adjusted odds ratio 0.73, 95% CI 0.64-0.99), but the dose-response relationship was not significant. In the literature review 17 studied populations from 11 studies were analysed; four demonstrated a significant association of fish consumption (or high verse low consumptions) with reduced risk of dementia, eleven showed a non-statistically significant reduced risk, and two exhibited no association (or increased risk). The meta-analysis from available data including the Chinese study showed a relative risk (RR) of 0.80 (95%CI 0.74-

0.87) of dementia in people with fish consumption, and the impact was similar among countries with different levels of income. Pooled dose-response data revealed a RR of 0.84 (0.72-0.98), 0.78 (0.68-0.90) and 0.77 (0.61-0.98) in people with low, middle to high consumption of fish. The matched figures for Alzheimer's disease (AD) were 0.88 (0.74-1.04), 0.79 (0.65-0.96) and 0.67 (0.58-0.78) respectively.

Conclusions: Greater consumption of fish is associated with a lower risk of dementia. Increasing fish consumption may help prevent dementia worldwide.

Keywords: Dementia, Alzheimer's disease, Fish consumption

Introduction

Dementia is one of the world's biggest health problems and is a major public health challenge that is becoming more common as the aged population grows. There are 47.5 million people with dementia in the world, and the number of people affected is predicted to rise to 131.5 million by 2050 [1]. There is no known cure for dementia, and thus more efforts have been made to investigate its risk or protective factors for prevention. Previous studies showed that eating fish has led to a reduced risk of cardiovascular diseases (e.g. coronary heart disease[2], stroke[3]) and respiratory disease[4], and benefited mental health (eg, preventing depression) [5, 6]. There are also some studies suggesting that fish consumption could improve cognitive function across life course[7] , particularly in young people[8] .

Since the fish fatty acids are important constituents for proper brain functioning and neurocognitive development [9], there has been an increase in investigating whether fish consumption could reduce the risk of dementia [10, 11]. However, the findings from those studies are not consistent [12-14]. Some studies suggested that the consumption of fish was associated with a reduced risk of dementia[15, 16], while others did not show such an association [17-20]. Due to its important topic in public health, some meta-analysis papers were previously published [21-23] to investigate the association of fish consumption with risk of dementia. However, those meta-analysis studies may not be performed properly, e.g. having missed some relevant published studies [10] in their literature review, and provided no solid conclusion about whether or not increased consumption of fish would reduce risk of dementia. Furthermore, the knowledge on the impact of fish consumption on the risk of dementia is predominately derived from studies undertaken in high income countries, and there is lack of data [22] from low and middle income countries (LMIC) to examine the association, where people have high risk of

dementia but low level of fish consumption[1]. The findings of the impact of fish consumption on the risk of dementia from previous research cannot be generalised to people living in LMICs. In this paper, we examined data of large-scale household health surveys from China and carried out an updated systematic world literature review and meta-analysis to investigate the association of fish consumption with risk of dementia and its dose-response relationship, and examine any differences in the association between high income countries and LMICs.

Methods

A multi-province health survey study of older people in China

We examined the data from the multi-province health survey study of dementia in China. The methods of the studied populations and interview outcomes have been fully reported before[24, 25]. In brief, during 2007-2010, we carried out a large-scale health survey study of older people in provinces of Guangdong, Heilongjiang, Shanghai and Shanxi, Anhui and Hubei in China to investigate prevalence, risk factors and care of dementia and other chronic conditions[25, 26].

The Four-Province Study: In 2008-2009 we selected one rural and one urban community from each of the four provinces (Guangdong, Heilongjiang, Shanghai, Shanxi) at the study fields. We tried to recruit no fewer than 500 participants in each community, and employed a cluster randomised sampling method to choose residential communities (the district in urban areas and the village in rural) from each of the four provinces. The target population consisted of residents aged ≥ 60 years living in the area for at least 5 years. Based on the residency list of the committees of the village and the district, we recruited a total of 4314 participants with an overall response rate of 93.8%. The local survey team interviewed the participants at home. The main interview included a general health and risk factors record, the Geriatric Mental State (GMS) questionnaire[27] and other components of the 10/66 algorithm dementia research package[28]. We carried out a two-phase interview to save our research resources. In phase one, we completed the general health and risk factors record, the GMS, the Community Screening Instrument for Dementia (CSI-D) cognitive test and Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Using three of the four constituent components of the 10/66 algorithm (i.e. data of GMS-AGECAT, the CSI-D cognitive test and CERAD interview), we calculated a probability of possible dementia for each participant. In phase two, we selected the

top 15% of the population who had the highest probability of having “dementia” as “probable cases” and a random sample of 5% of the rest as “probable non-cases” for subsequent interviews in each province. The interview team completed the CSI-D informant interview for the selected participants.

The Anhui study: Using the same interview approach as those in the 4-province study, we completed interviews of 1757 older people from the 3rd wave survey of the Anhui cohort[25], the initial number of which was 3336 participants aged ≥ 60 who were randomly recruited in 2001 and 2003 respectively.

The Hubei study: In 2010-2011 we extended the project to include the Hubei province[25]. We used the same protocol and interview materials as the Four-province study, but interviewed all participants at one stage phase using the full 10/66 methods. We recruited 1,001 participants aged ≥ 60 years. In the six provinces, the overall response rate from the interview was 98.7%.

Risk factors: In the general health and risk factors questionnaire interview, we recorded details relating to socio-demography, lifestyle, social networks and support, histories of chronic diseases and risk factors[29]. We measured height, weight, waist circumference and blood pressure for all participants. In the interview, we asked each participant for details of dietary intakes, including rice, wheat flour, meat, fish, egg, fresh vegetable, fruit, chilli pepper, garlic, ginger and different types of vegetable oils. All participants were required to provide the answers to the frequency of fish consumption in the past 2 years: *Never eat, Once a week, More than twice a week, Once a day, and \geq Twice a day.*

Diagnosis of dementia: The GMS data were analysed by a computer program-assisted diagnosis, the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT), to assess

the principal mental disorders in the study participants[27]. We employed the 10/66 dementia algorithm to diagnose dementia, which included the data from the GMS-AGECAT diagnostic output, the CSI-D, COGSCORE, the CSI-D informant interview (RELSCORE), and the CERAD ten-word list learning task with delayed recall [28, 30]. We used a cut-off point of probability (≥ 0.25) derived from the full 10/66 algorithm to diagnose dementia, which has been validated in China. 326 participants were diagnosed to have dementia.

Data Analysis

We employed a binary logistic regression model to examine odd ratios (ORs) and their 95% confidence intervals (CIs) of dementia in participants with different levels of fish consumption in comparison to those with no fish consumption in the past 2 years. In the model, we adjusted for age, sex, province, urban-rural areas, education level, smoking status and stroke. The data analysis was run in SPSS (version 20).

Systematic literature review

We (Aishat T Bakre, Ruoling Chen, Isaac M Danat, and Weiju Zhou) searched literature from databases of Medline, PubMed, CINAHL, Psych-info and Psychology and Behavioural Sciences Collection. The strategy for the database search was developed using the Population, Exposure and Outcome framework (PEO) [33]. The search terms were [“dementia” OR “Alzheimer’s disease”] AND [“fish”]. The literature was searched from the earliest dates of each of the databases to 30th November 2016. The search for relevant articles included all studies with no language restriction. We read the title and abstract of the searched studies. The studies selected were appropriate for this review if they investigated an association between fish consumption

and dementia (or Alzheimer's disease) in the population. Alongside the electronic database search explored, a manual reference search was also conducted to find possible extra articles. If two articles were published from the same cohort data but in different follow-up durations [20, 31], we would use the longest follow-up study paper for review. [20] Figure 1 shows the study selection process. We identified 11 original studies eligible for review. Following the PRISMA [32] guidelines, we (Aishat T Bakre, Gordon Qin, Isaac M Danat, and Weiju Zhou) conducted a systematic review. Each of the articles was reviewed by two reviewers and assessed independently using a predesigned data extraction form to extract the necessary information from the chosen studies. The quality assessment of the articles was achieved by employing the Newcastle-Ottawa Scale[33].

Meta-analysis

Data were pooled from identified studies, which provided the relative risks and 95% CIs, and the 6-provinces study. We analysed the data using each of studied populations as analysis unit, to investigate all types of dementia and then AD in relation to the consumption of fish. A random effect model was employed if the heterogeneity of the within and between studies variation were significant; otherwise a fixed effect model was used. The publication bias was evaluated using the Egger's regression [34]. First, we tried to assess an overall relative risk of dementia in participants who consumed fish in comparison with those who did not from all eligible studies; if the article only gave the RRs in different levels of fish consumption we took the figure from the highest level group for pooling data analysis, and if the article only gave the figures from the continuous data analysis of fish consumption or from only high vs low levels of fish consumption, we took them in the meta-analysis. Second, we stratified the identified studies for

meta-analysis according to the number of the groups of fish consumption levels. This would help to examine differences in the RR among studies with different level of fish consumption data analysis. Third, we investigated a dose-response association between the fish consumption and the risk of dementia according to low, middle and high consumption verse never/rare consumption. When the article only gave the figures from the continuous data analysis of fish consumption or from only two groups of fish consumption (high vs low level) we took them in the middle level of fish consumption for the meta-analysis, while if the article only gave the figure from the middle and high levels of fish consumption verse no/rare consumption we took them in the middle and high group levels for pooling the data. We examined any differences in the impact of fish consumption on the risk of dementia among LMICs and high income countries, and also investigated any influence of the study design (cases-control studies, cross-sectional studies, and cohort studies) and duration of the cohort follow up on the association. All analyses were performed in the STATA (version 14.2 software StataCorp).

Results

The six provinces study of China

Of 7072 participants, 6981 (98.7%) provided information on fish consumption. Their average age was 62.6 ± 12.2 years, and 54.x% were women. 1528 participants (21.9%) did not eat fish over the past 2 years, 2631 (37.7%) consumed fish once a week, 1938 (27.8%) \geq twice a week and 884 (12.7%) at \geq once a day. [The data of risk factors in each of these four groups are included in our other paper prepared, not shown here]. Table 1 shows numbers, percentages and ORs of dementia in participants with different levels of fish consumption. The risk of dementia

decreased with increased consumption of fish, although participants with fish consumption at \geq once a day had the highest prevalence of dementia (6.6%). After adjusting for age, sex, stroke and other confounding factors, we found that participants with different levels of fish consumption had a reduced risk of dementia (Table 1). Compared to those not eating fish over the past two years, participants with any level of fish consumption had a 27% significant reduction in the risk of dementia (adjusted OR 0.73, 95% 0.64-0.99).

Systematic literature review

In 11 studies identified for this literature review, which were published between 2002 and 2011, we found that all were conducted in high income countries (except for one study led by the UK [35] which included 7 studied populations from LMICs). One of the studies was cross-sectional [35], 3 were case-control [11, 36, 37] and 7 were cohort [10, 15, 16, 20,38-40]. These articles included 17 studied populations (one study[35] covered 7 populations). Their sample size varied from 57 to 14956, with a total of 33964 participants, and the minimal age in these studies population varied from 55 to 76 years. Four of the studied populations showed a statistically significant association of fish consumption with reduced risk of dementia (the magnitude of the association varied from 20% to 60%, although two of them [36, 37] reported a significant association but did not reveal the association figures. Eleven suggested an association but a non-statistically significant reduction, while two exhibited no association (or increased risk) [20, 35]. Online Table 1 documented the details of the studies' characteristics and outcomes and the narrative review for each of these studies were shown in Appendix 1. We also reviewed and examined the quality of each of these studies and found that the quality of these articles was in

general good (Table 5), and would include them for meta-analysis if the necessary data was provided.

Meta-analysis

After excluding two studies that did not provide the relative risk (RR) data, [36, 37] we took data from above 15 studied populations and the data from the 6-provinces study of China for the meta-analysis. In total, there were 40,668 participants, with a number of 3139 dementia cases for analysis. A forest plot of the findings from these studied populations can be seen in Figure 2. The fixed effect model analysis showed that there was a 20% reduction in the risk of dementia in participants with the consumption of fish (or at higher level) versus those not eating fish (or at a lower level). There was little evidence of publication bias; the Egger method of bias estimate showed a p-value of 0.597 (online Figure 1). From the 7 studies which examined the risk of AD in relation to fish consumption [10, 15, 16, 20, 38-40], the pooled data (in total 1105 cases of AD) showed a significant association between fish consumption and reduced risk of AD (RR 0.73, 95% CI 0.65-0.82).

Data analysis for studies with different level of fish consumption showed no significant differences in RR for dementia in relation to fish consumption (Table 4). The findings of AD data analysis (online Table 4) were similar to those in Table 4.

In the subgroup data analysis (Table 2), we observed that the impact of fish consumption on the risk of dementia was similar in people from LMICs and from high income countries. We also found that the magnitude of the association between fish consumption and the reduced risk of dementia was similar among those cross-sectional studies, short-term follow-up cohort studies and long-term follow-up cohort studies (Table 2). The patterns of these associations in AD were similar (online Table 2).

In 16 studied population from 9 articles which included the dose-response data [11, 15, 16, 20, 38-40], 2 studied populations showed a significant trend. The pooled data showed a reduced RR of 0.84 (0.72, 0.98) in dementia in participants with low level of fish consumption, of 0.78 (0.68, 0.90) in middle level of fish consumption, and of 0.77 (0.61-0.98) in high level of fish consumption (Table 3). The matched findings for AD were 0.87 (0.74-1.04), 0.79 (0.65-0.96) and 0.67 (0.58-0.78) respectively (online Table 3).

Discussion

Our study examined the data of large-scale health survey of dementia in China and completed a worldwide systematic literature review and meta-analysis to assess the impact of fish consumption on dementia risk. We have found that increased consumption of fish was significantly, and dose-dependently associated with reduced risk of dementia and AD. The impact of fish consumption on reduced risk of dementia remains in low and middle income countries and high income countries.

It is not surprising for us to observe the reduced risk of dementia in relation to fish consumption. Fish is the major dietary source of omega-3 polyunsaturated fatty acids (PUFAs), which comprise of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), being collectively called the fish fatty acids[41-43]. Previous studies have suggested the preventive effect of fish consumption and its constituent (omega-3 fatty acid) on cardiovascular disease, through inflammation reduction, blood pressure reduction and endothelial function enhancement [3]. In a health professional 12 years' follow-up study of 43671 men aged 40-75 years in the USA, He et al [44] identified the beneficial effect of fish consumption on the risk of stroke with a RR of (0.54, 95% CI 0.31 to 0.94) for those who consumed fish for ≥ 5 times per week [44]. In a large-scale study of the National Health and Nutrition Examination Survey I (NHANES I), Gillum et al [45] found that black population with any fish consumption level had a 49% significant reduction in the risk of developing stroke (RR 0.51, 95% CI 0.30-0.88). The fish consumption has been shown to have a preventative effect on reducing the risks of coronary heart disease, respiratory disease and cancer. These are co-morbidities associated with dementia [46-48]. Therefore, it is

possible that reducing these diseases may be one of the pathways of the preventive impact of fish consumption on dementia.

Strengths and Limitations of the study

The main strength of this paper is the inclusion of a large scale health survey from China and all studies of topic-related worldwide literature to investigate the association of fish consumption with the risk of dementia. Older Chinese citizens have higher levels of socioeconomic deprivation, but low levels of cardiovascular risk factors (e.g. obesity) and depression. These special population characteristics of older Chinese residents helped to assess the association of fish consumption with the risk of dementia. Our systematic literature review and meta-analysis have focused on determining the association between fish consumption and risk of dementia and identifying differences in the association among LMICs and high income countries. The previous meta-analysis papers [21-23] investigated the associations of both fish and omega-3 PUFA with combined mild and severe cognitive impairment (e.g. Mild cognitive impairment (MCI), Parkinson disease (PD), dementia and Alzheimer's disease), not specifying exposure or outcomes, and failed to include some relevant studies [10]. In comparison with those three earlier reviews and meta-analyses [21-23], our systematic review and meta-analysis have elaborated specifically on the impact the consumption of fish has on dementia and AD development. Our findings were based on the literature search without any limited selection and identified all eligible studies further including a new study from China (LMIC), which

compensated for the scarce data from the LMIC countries, making a more generalized association. Adding in the new study from China made our meta-analysis findings more robust.

Our study has limitations. Firstly, our 6-province health survey data was cross-sectional, and its causal-relationship between fish consumption and dementia risk could not be assessed. However, the findings of the study were similar to those in the cohort studies [10, 15, 16, 20, 38-40]. Secondly, the 6-province survey did not include different type (lean, fatty-fish, fried fish and seafood) and amount of fish consumed by participants for analysis, and also there was lack of data on the different types and amounts of fish consumed in the majority of existing literature on this topic. This may dilute our findings of the association between consumption of fish and the risk of dementia. We could not examine the impacts of different types and amounts of fish consumed on dementia risk, which needs further investigation in future. However, it seems that eating fish is related to PUFAs, which benefit health. Thirdly, the identified articles used different levels of the fish consumption for data analysis, making it difficult to assess the overall effect in people with eating fish verse those not eating. Unlike our previous meta-analysis [49], we could not convert their findings from the fish consumption groups as a combined finding into one group of the fish consumption. Using the RR data from the highest level group of fish consumption in some studies may be over-estimating the overall effect of fish consumption on dementia risk. However, when we stratified the articles for meta-analysis according to the number of the groups of their fish consumption level, we did not find that there was a trend of reduced risk of dementia or AD with increased number of the fish consumption level groups (Table 4, and online Table 4). If we included all RRs from different levels of fish consumption to pool the data (online Figure 2), the finding of the overall effect was not substantially changed (0.80, 0.75-0.87). Fourthly, in the meta-analysis two of the three case-control studies did not

provide the necessary data for analysis, and thus we could not pool the data from the case-control studies to compare with those in the cross-sectional studies and the cohort studies. Also, the numbers of the studies which were used for the subgroup analysis are small, and we should be careful to interpret no differences in the impact of fish consumption on dementia risk among those sub-groups.

In this systematic literature review we have noted that these 11 identified articles plus the 6-province study had various study designs, different locations, and various types of food frequency questionnaires to measure their fish intake. The outcome of the current study was examined using the review guidelines of Bradford Hill [50], to provide a comprehensive indication of a causal association between consumption of fish and risk of dementia or AD.

How strong are the associations?

The majority of the identified studies have shown a moderate to high association of fish consumption with the risk of dementia with a variation of between 20% to 60% [10, 11, 15, 16, 20, 35, 38-40] after adjusting for possible confounders. Only a few showed a weak or no association between fish consumption and the risk of dementia [20]. Our pooled data analysis showed a 20% to 30% increase in the risk of dementia and AD in people who did not eat fish in comparison with those eating fish. The magnitude of the association between fish consumption and the risk of dementia is similar to the impacts of environmental tobacco smoke (ETS) on the incidence of coronary heart disease (25% increased risk [51], and on lung cancer (27% increased risk [52]), which both have been taken as the causal relationship with ETS exposure.

How consistent are the reported studies?

Of the 17 studied populations in this paper, 15 reported consistent evidence of a reduction in the risk of dementia after a moderate to high intake of fish and adjusting for possible confounders [10, 15, 16, 36-40]. Two of the studies also showed a positive significant association with the risk of mild to severe dementia and AD development, when the plasma phospholipid and the serum level of the AD participants were assessed for their DHA and EPA level [36, 37]. A significant reduction was also observed in the 6-province study from China. A consistently inversed association between fish consumption and dementia risk was observed in all seven countries except India that took part in the 10/66 dementia research group' study [35]. Our meta-analysis for these reviewed studies showed a high level of homogeneity, suggesting their consistent data.

Moreover, there are similar findings of the impact of fish consumption on cognitive function in children. Cohen et al [53] analysed the data of a randomized control trial (RCT) and demonstrated a 0.13 points increase in the intelligence quotient (IQ) of children when mothers were supplemented with an increase intake of 100mg/day of DHA. A review by Eilander et al [8] established an enhanced cognitive development in infants and children after maternal supplementation with omega-3 long-chain polyunsaturated fatty acids (LCPUFA) during pregnancy and lactation but have inadequate evidence for children >2years old. Ryan et al [54] in their review also indicated that neurocognitive development during childhood is enhanced

when pregnant and lactating mothers are supplemented with DHA. These would support our findings of the impact of fish consumption on reduced risk of dementia.

How specific are the proposed fish consumptions and the response to outcome?

Of these identified papers, a few studies [15, 38, 39] investigated the fish intake based on fatty, lean, fried fish and seafood. The consumption of these types of fish might have affected the outcome of these studies. The association identified from the systematic literature review was significant, showing a positive effect on the risk of developing dementia and AD in the majority of the studies. Huang et al [39] revealed a 28% reduction in the risk of developing dementia after intake of fatty fish, while the consumption of lean fried fish produced no significant beneficial effect. The two major fish constituents (DHA and EPA omega-3 fatty acids) were associated with a reduced risk of developing dementia and cognitive decline [21, 43]. The dose-response impact of fish consumption on specific dementia, i.e., AD seemed to be stronger.

Is there a temporal relationship between exposure and response?

The observed association between fish consumption and dementia was prominent in all the prospective cohort studies [10, 15, 16, 20, 38-40], demonstrating a temporal association which signified that an exposure preceded the outcome. In the United State, Huang et al [39] followed up 2233 participants for 5.4 years and identified 378 new cases of dementia; the RR in participants with fish consumption was 0.79 (0.53-1.20). The Rotterdam study followed up 5395 participants for 9.6 years and observed 465 dementia developed, showing a RR of 0.95 (0.76-

1.19) of dementia in relation to fish consumption [20]. The pooled data of RR between short and long-term follow up studies were similar (Table 2, seen in Results section)

Is there an exposure-response relationship?

An exposure-response relationship has been identified between different levels of fish consumption and risks of dementia and AD, in our meta-analysis and in the majority of identified studies [17, 18, 21, 24, 37, 40-44]. Morris et al [16] demonstrated a non-significant dose response relationship; RR of AD in participants who consumed fish 1-3 times per month was 0.6(0.3-1.3), and a significant relationship in those who consumed fish at once a week 0.4(0.2-0.9), and in participants who consumed fish at ≥ 2 times per week 0.4(0.2-0.9). However, other cohorts studies [15, 38, 40] showed that in the highest level of fish consumption the reduced risk of dementia was not significant, and these may be due to the small number of patients in this group. Nevertheless the pooled data in our paper (Table 3) across all the different level of fish intake from the included studies, have shown a significant reduction in the risk of dementia and AD (Online Table 3).

Is the association biologically plausible?

The biological mechanism exhibited by fish consumption in relation to the prevention of dementia, may be as a result of the presence of omega-3 fatty acid as part of their constituents.

The omega-3 fatty acid is a major component of neuronal membranes, with a cardio-protective, anti-inflammatory, antioxidant and anti-atherogenic properties[41, 55, 56]. They have the capability to display a beneficial effect on the risk of developing Alzheimer's disease and dementia, particularly vascular dementia[17, 31, 38]. Fish has a beneficial source of essential amino acids, micronutrients and vitamins, thus increasing the protective effect they exhibit on the risk of developing all cause dementia and cognitive impairment [57]. Fatty fish are known to be richer sources of DHA and EPA, which are naturally found in trout, tuna, salmon, sardines, herring [58], and mackerel, but minimal sources are found in lean fishes, such as cod, haddock, and halibut. An increase in the intake of fatty fish may be positively associated with a decrease in the level of the consumption of saturated fat, thus reducing the risk of stroke[3]. This might be as a result of the anti-inflammatory, antithrombotic, antioxidant and anti-amyloid properties of its omega-3 fatty acids component [42, 55, 56].

Is the evidence coherent with knowledge of the natural history of disease?

Dietary fatty acid has displayed a significant effect on the risk of developing cardiovascular disease, [42, 59, 60] depression [5] and children's cognitive impairment [8, 61]. This association involves the higher consumption of saturated fat and cholesterol and lower consumption of polyunsaturated fatty acid, which is omega-3 fatty acid-one of the fish constituents. Omega-3 fatty acid intake has been associated with reduced risk of cognitive impairment and dementia through several possible mechanisms. They display a cardio-protective property that makes them protective over several cardiovascular risk factors such as stroke, atherosclerosis, and inflammation through influence on brain development and proper membrane function [31, 62]. They have exhibited their cognitive-enhancing effect during infancy, childhood, old age and

among adult with neurocognitive impairments in some clinical trials [62, 63]. This beneficial effect was supported by the outcome of the Chicago Health and Aging six years' prospective cohort study (CHAP) that involves fish intake and cognitive impairment [12], and in the result revealed in the Zutphen Elderly five years' prospective cohort study of fish consumption, omega-3 fatty acid and cognitive decline [13]. The China health and nutrition survey also maintained that adequate intake of fish does lowered cognitive decline [64]

Is there experimental evidence?

Numerous animal studies have demonstrated the positive role that omega-3 fatty acids (a fish constituent) played on brain development. They increase neurotransmission [55, 65], enhance memory capabilities [66-68], enhance the excitability regulation of the neuronal membrane [69] decrease the neurons ischemic damage [70] and increase the cerebral flow of blood [71, 72]. Experimental animal that had a reduced level of DHA in their diet exhibited an impaired cognitive function, while those animals that had a prolonged administration of DHA demonstrated an enhanced gain in memory [73]. These studies confirmed that the exposure of animal models to the intake of DHA produced an uninterrupted influence on their neurological status.

Does the evidence accord by analogy with that from other fields?

Previous studies showed a significant beneficial effect of intake of omega-3 fatty acid on dementia and cognitive impairment [12, 13]. Finding from a randomized control trial (RCT) that involved supplementing the treatment group with arachidonic acid (ARA) and DHA, part of

omega-3 fatty acids components, did exhibit a significant beneficial effect on the cognitive function in the treatment (mild cognitive impairment (MCI-group), while the placebo group showed no significant beneficial effect [74]. A similar beneficial effect was observed among the MCI participants in a RCT of 46 participants of (23 mild or moderate AD and 23 MCI) that were randomized into omega-3 PUFA acids treatment group and olive -oil placebo group [75]. In an one-year RCT that investigated the effects of fish oil supplementation on cognitive function in older adults Lee et al [76] found a significant beneficial effect within a short-term on participants working memory, immediate verbal memory and in the delayed recall ability among the treatment group that were supplemented with fish oil. The results of this current study are thus consistent with the findings of these studies, thereby acknowledging the positive influence that fish and its constituents have on cognitive function.

Implication of the study findings

As the world population ages the epidemic of dementia has become a public health problem. In 2015, over 47.5million people in the world were estimated to be living with dementia, with an increment of twice the figure every 20 years and a prediction of 131.5 million cases by the year 2050[1]. The majority of the increment is expected to be in the LMICs, which currently hold 63% of people living with dementia, with further increment by the year 2050 [1]. In China there is an increasingly growing number of dementia due to its population of older people with mixed characteristics (i.e. low levels of education and socioeconomic status but rapid increased income) [77]. Since there is no effective treatment on dementia, it is important for us to prevent dementia.

Our study has shown the significant association of high fish consumption with reduced risk of dementia. It displays a significant beneficial effect of eating fish on reducing dementia. Our study has increased awareness about the importance of consuming fish in population, helping reduce the risk of dementia worldwide. At present, the global per capita fish consumption level is estimated to be an average of 20 kg per year[78], and is lower in the low and middle income countries (18.8 kg) than those in high income countries (26.8kg). Our study demonstrated consistent findings of the impact of fish consumption on the risk of dementia between LMICs and HICs. Thus, we urge that people in LMIC should increase fish consumption to reduce the burden of dementia. People should increase their level of fish intake, especially in areas where the consumption is quite low. If this increment is maintained across all the continents, it will ensure people worldwide are consuming enough fish that will reduce the risk of dementia.

Contributor Statement

Aishat T Bakre: searching and reviewing the topic related literature, carrying out the meta-analysis, and drafting and revising the manuscript.

Harry HX Wang and Li Wei: analyzing the data of Chinese study, interpreting the findings, and commenting the manuscript

Jiaji Wang: study concept, coordination and data collection and analysis design of the Chinese study

Gordon Qin, Isaac M Danat, and Weiju Zhou: involving literature search and reviewing the identified articles

Ranjit Khutan, Tina Smith, Peter Schofield, Angela Clifford, Arpana Verma, Cuilin Zhang: critical reviewing the manuscript, interpreting the data, and revising the manuscript

Ruoling Chen: study concept and design, study supervision, and drafting and revising the manuscript.

All authors checked, interpreted results and approved the final version,

Competing Interests

The authors have no competing interests to declare.

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Table 1: Numbers, percentages and odds ratios (95% confidence intervals) of the level of fish consumed by people with dementia according to their demographic characteristics and socioeconomic status: the six-province study in China

Frequency of fish consumed over the past 2 years	Dementia					Multivariate-adjusted			
	No		Yes			analysis			
	n	(%)	n	(%)	<i>P</i> *	OR [†]	95%CI		<i>P</i> [‡]
Fish									
No	1438	94.1	90	5.9	<0.001	Ref.			
Once a week	2516	95.6	115	4.4		0.79	0.49	1.29	0.355
More than twice a week	1875	96.7	63	3.3		0.59	0.38	0.90	0.014
>=once a day	826	93.4	58	6.6		0.76	0.55	1.04	0.089
<i>Total</i>	<i>6655</i>	<i>95.3</i>	<i>326</i>	<i>4.7</i>					

*Chi-square test P value. [†]Adjusted for age, sex, province, urban-rural areas, education level, smoking status and stroke.

[‡]Overall P value for the variable.

Table 2: The pooled analysis results for Fish Consumption and Dementia Risk

Variable for subgroup data analysis	Nos of Studies	Nos of Studied populations	Participants	Dementia cases	RR (95% CI)
Country of study					
Low and middle income [1] and the six-province study of China	2	8	21,937	1671	0.79 (0.72 -0.88)
High income [2-8]	7	7	17916	1468	0.83(0.71- 0.97)
Design of study					
Cross-sectional studies[1] and the six-province study of China	2	8	21,937	1671	0.79 (0.72-0.88)
Cohort studies (follow up ≤ 5 years) [5, 8]	2	2	8327	323	0.67 (0.38-1.18)
Cohort studies (follow up >5 years) [3, 4, 6, 7]	4	4	9,532	1112	0.85 (0.72-1.00)

Abbreviations: CI: Confidence Interval; RR: Relative Risk.

Table 3: Dose-Response Relationship between Fish Consumption and Risk of Dementia

Level of Fish Consumed	Nos of Studies	Participants	Dementia cases	RR (95% CI)
Low consumption [2, 3, 5-7] and the six-province study of China	6	23,239	Dementia (1582)	0.84 (0.72-0.98)
Middle consumption [2-6, 8] and the six-province study of China	7	24,409	Dementia (1695)	0.78 (0.68-0.90)
High consumption [3, 5] and the six-province study of China	3	17,299	Dementia (985)	0.77 (0.61-0.98)

Abbreviations: CI: Confidence Interval; RR: Relative Risk.

Table 4: Data analysis for different Level of Fish Consumption

Data of fish consumption level in study	Nos of Studies	Nos of Studied populations	Participants	Dementia cases	RR (95% CI)
Continuous [1-8] and the six-province study of China	9	15	39,853	3,139	0.80 (0.74-0.87)
Only 2 levels [7]	1	1	488	99	0.61(0.28-1.33)
Only 3 levels [2, 4, 6, 8]	4	4	7,110	710	0.86 (0.71-1.03)
4 levels [3, 5] and the six-province study of China	3	3	17,299	985	0.77 (0.61-0.98)

Abbreviations: CI: Confidence Interval; RR: Relative Risk.

Table 5: Systematic Literature Review Quality Assessment for cohort studies of “fish consumption and the risk of dementia”

Study	1	2	3	4	5	6	7	8	9	10
Albanese et al[1]	★	★	★		★	★	★	★	★	★
Tully et al[11]	★	★	★	★	★			★	★	
Conquer et al[12]	★	★	★	★	★			★	★	
Kim et al[2]			★		★		★	★	★	★
Barberger-Gateau et al[5]	★	★	★	★	★	★	★	★	★	★
Lopez,et al[8]		★	★		★	★	★	★	★	★
Morris et al[10]	★	★	★	★	★	★	★	★	★	★
Schaefer et al[7]	★	★	★	★	★	★	★	★	★	★
Devore et al[6]	★	★	★	★	★	★	★	★	★	★
Barberger-Gateau et al [4]	★	★		★	★	★		★		★
Huangs et al [3]	★	★	★	★	★	★	★	★	★	★

Cross-sectional Studies

1- Aims/objectives of the study clear and study design appropriate for the stated aim(s)

2-The sample size justified

3 -Sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation.

4- Selection process likely to select subjects/participants that were representative of the target/reference population under investigation.

5- The exposure and outcome variables measured correctly using instruments/ measurements that had been trialled, piloted or published previously.

6. Data analysis controlled for age, sex and education

7-Data analysis controlled for other confounders

8-Findings interpreted well

9- Weakness mentioned and explained clearly

10-Paper written well

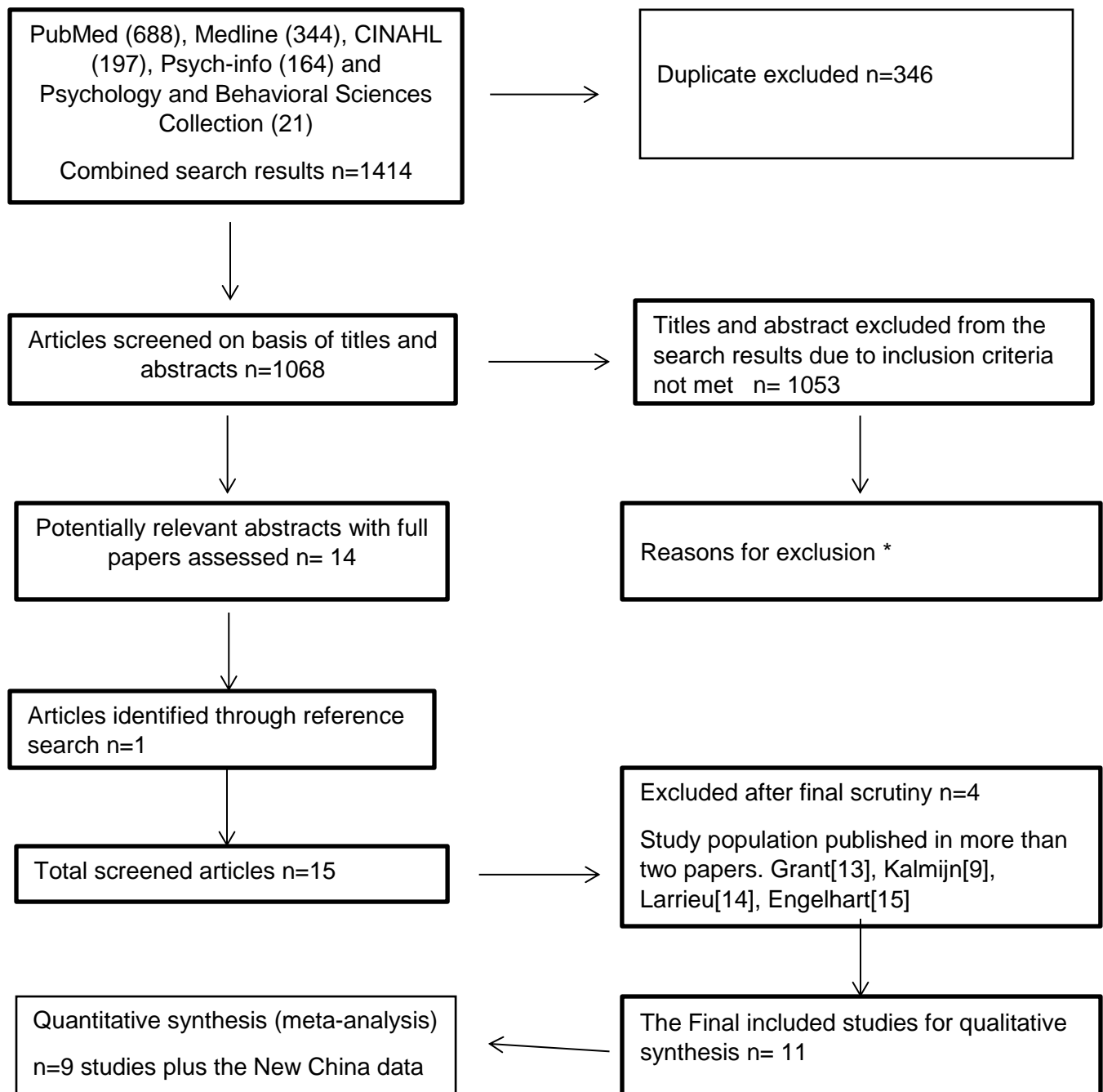
Cohort Study

- 1 – Cohort truly representative
 - 2 – Controls derived from the same cohort
 - 3 – Clear measurement of fish consumption at baseline
 - 4 – Adequacy Follow-up duration (≥ 12 months)
 - 5 – Reliable methods of dementia and AD diagnosis (ie, Quality of outcome)
 - 6 – Cohort data analysis controlled for age, sex and educational level
 - 7 – Cohort data analysis controlled for other confounders
 - 8 – Findings interpreted well
 - 9 – Weakness mentioned and explained clearly
 - 10 – Paper written well
- N/A = Not applicable

Case-Control Study

- 1- Is the case definition adequate? (yes, with independent validation)
- 2- Representativeness of the cases
- 3- Selection of controls (community controls)
- 4- Definition of controls (No history of the disease)
- 5- Clear measurement of fish consumption (clear records or structured interview and with same for both cases/controls)
- 6- Data analysis controlled for age, sex and educational level
- 7- Data analysis controlled for other confounders
- 8 - Findings interpreted well
- 9 -Weakness mentioned and explained clearly
- 10 -Paper written well

Fig1: Diagrammatic expression of the literature search technique



*Appropriate outcome not reported, Randomized control trial; Assessed another exposure other than fish, Assessed another outcome other than dementia or AD, Articles on importance of fish to dementia and brain development, News briefs, Articles on elderly nutrition, Systematic review/meta-analysis, Presentation

Forest plot showing the pooled estimate results of all the included studies of dementia Risk

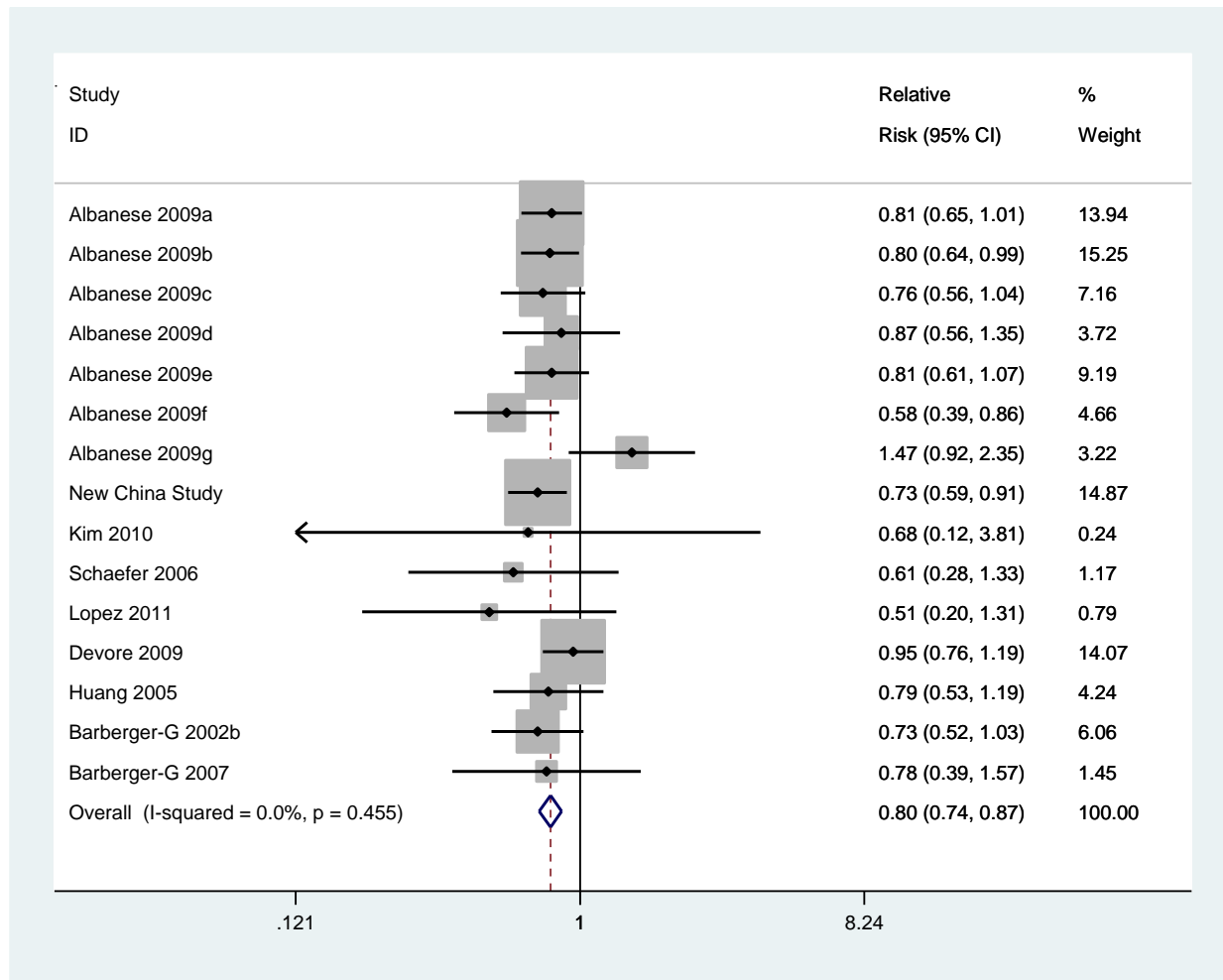


Fig.2: Forest plot showing the association of fish consumption and dementia risk

Reference

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